

## REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1, 2, 3, 4 and 29 were amended by inserting “at least one isotope of a transition element”. Claim 20 was amended by replacing “element” with “isotope”. Claims 22-27 were amended by replacing “element” with “tag”. Claims 5, 6, 10-14, 20 and 22-24 were amended to remove multiple dependencies and reduce the claim number in compliance with the “5/25” rule. Claims 19 and 28 were canceled.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-14, 20-27 and 29-36 are now pending in this application, of which claims 30-36 are withdrawn.

### **Claim Rejections under 35 U.S.C. § 103(a)**

The Supreme Court has recently reaffirmed the *Graham* factors for the determination of obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. \_\_\_, 127 S. Ct. 1727 (2007). These four factual inquiries under *Graham* are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 17-18 (1966). In accordance with these factors, to establish a *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Further, the Court still requires that the reasoning used to combine the elements in the fashion claimed be made explicit. *KSR*, 550 US at \_\_\_\_\_. Applicants assert that this burden has not been met.

The Examiner has rejected the claims under 35 USC § 103(a) as unpatentable over the combinations of Cais (US Patent 4,205,952), Foster et al. (US Patent 4,444,879), Maggio (Immunoenzyme Technique I, 1980), Nielsen et al. (Spectrochimica Acta, 1998), Houk et al (Analytical Chemistry, 1980, Vol. 52, pages 2283-2289, Crooke (WO 99/451450) and Mire-Sluis et al (Journal of Immunological Methods, 186, 1995, pages 157-160). Applicants respectfully traverse this rejection.

***I. Cais in view of Foster***

The Examiner alleges that claims 1-5, 10-14 and 20-21 are obvious in view of Cais and Foster. Cais discloses a method of tagging biologically active materials with metals. The Examiner further states that Cais also discloses kits (at column 11, lines 45 to 58). The Examiner states that it would have been obvious to combine Cais with Foster to develop kits as claimed in the present application. The Examiner explains that “the printed matter on instructions merely teaches the use of an existing product, and thus cannot impart patentability”.

Applicants amended claims 1, 2, 3, 4 and 29 by inserting the term “at least one isotope of a transition element”. Support for this term is found throughout the specification and in particular in paragraph [0072], [0140] and [0145].

*(i) The prior art does not teach every element of the claimed invention*

The amended claims include “a tag comprising at least one isotope of a transition element for directly tagging a biologically active material”. Cais did not disclose any isotopes, because his method of analysis could not detect isotopes. Cais taught the analysis of tagged molecules using atomic spectrometry (see, for example, column 4, line 50; column 5 lines 48-55; column 7, line 1; column, 12 line 8), and taught away from mass spectrometry due to “various degrees of non-specificity and interferences cause that these techniques could not be practically applicable” (see column 1, lines 28-36). Atomic spectrometry cannot detect isotopes. Foster is directed to an immunological assay for testing immunoglobulin in a biological fluid. The reaction can be tested visually or by a “simple spectrophotometer” (see column 6 lines 36-39). Accordingly, Foster does not disclose the analysis of isotopes. Neither Cais nor Foster disclose or teach a kit comprising an isotope of a transition element.

Accordingly, all the claim limitations are not taught in the cited references. Applicants request that the rejection be withdrawn.

*(ii) There is no rationale supporting such a combination*

As published in the KSR Guidelines (72 Fed. Reg. 57526 (October 10, 2007), there must be a rationale supporting the combination of references in an obviousness rejection. Applicants assert this burden has not been met as such a combination of very different methods would not have been expected to succeed, much less arrive at method of the present invention.

Cais discloses a method of tagging biologically active materials with elements, including transition elements. The tagged biologically active materials are complexed with ligands in a heterogeneous specific binding assay. The elements are detected in a variety of detection systems including an emission spectrophotometer. Among other features, Cais differs from the instant application in not teaching the detection and measuring of an isotope of a transition element by an inductively coupled plasma mass spectrometer or inductively coupled plasma optical emission spectrometer.

Foster is directed to an immunological assay for testing immunoglobulin in a biological fluid. Foster teaches the testing of blood or other biological samples from patients for allergic reactions in a doctor's office. The reaction can be tested visually or by a "simple spectrophotometer" (see column 6 lines 36-39). Foster is also directed a process for coating light-transparent, water insoluble polymeric surfaces so that they remain optically clear yet become chemically reactive so that immunoreagents can be covalently bound to the surface (see column 3 lines 55 to 59) and an article for immobilizing reactants thereof (see claim 8). Accordingly, Foster et al. does not teach anything about inductively coupled plasma mass spectrometry or inductively coupled plasma optical emission spectrometry. Foster et al. teaches only the use of the immunoassay with a "simple spectrophotometer". A spectrophotometer differs from a spectrometer in that (i) it is usually a simple desk top instrument compared to a large, complex instrument and (ii) the range of wavelengths that can be assayed by a spectrophotometer is limited to visible light, near-ultraviolet and near

infrared compared to the spectrometer which covers a wide range of wavelengths, from gamma rays and X-rays into the far infrared.

Further, Foster et al. uses a chromogenic reagent to measure the reaction (see item 18 in Figure 4 and columns 9 and 10). The kit includes the chromogenic reagent (see column 15 lines 25 to 30. No chromogenic reagent is used in Cais or the present invention.

Further, the assay described in Foster et al. detects and measures reagents at the molecular level whereas the assay described in Cais detects and measures reagents at the atomic level.

Further, Cais detects and measures metal atoms bound to reagents, where Foster et al. does not disclose, teach or suggest anything about metal atoms.

In support of the difficulty in combining these methods, Cais was published in 1980 and Foster et al. was published in 1984. The solution provided by the present invention is not obvious, since within 17 years from the publication of prior art until the priority date of the present application, the experts in the field failed to provide it.

As the cited combination of references do not arrive at the present invention, nor is there a rationale supporting such a combination, Applicants assert that the claimed invention is nonobvious and the rejection should be withdrawn.

***II. Maggio:***

The Examiner rejected to claims 6-9 on the basis of obviousness with regard to Cais in view of Foster et al. and Maggio. Maggio discloses a solid reagent immobilization immunoassay. As discussed above, the claims are not obvious with regard to Cais and Foster because neither Cais nor Foster provide kits with isotopes of transition elements for tagging biologically active materials. Maggio does not teach kits having isotopes for the analysis of biologically tagged materials. Accordingly, the cited references do not provide all the elements of the amended claims. Applicants request that the rejection be withdrawn.

***III. Neilson:***

The Examiner rejected to claim 29 on the basis of obviousness with regard to Cais, in view of Foster and Neilson, stating that Neilson discloses laser ablation followed by analysis by ICP-MS.

Neilson discloses a method to identify serum proteins that naturally bind metals (cobalt). There was no intention to label biological materials or analytes that do not normally bind metals, with transition elements. As discussed above, the claims are not obvious with regard to Cais and Foster because neither Cais nor Foster provide kits with isotopes for the analysis of biologically tagged materials. Neilson does not teach kits having isotopes for labeling biologically active materials. Accordingly, the cited references do not provide all the elements of the amended claims. Applicants request that the rejection be withdrawn.

#### ***IV. Houk***

The Examiner rejected to claims 19 and 23-25 on the basis of obviousness with regard to Cais in view of Foster and Houk et al. Houk et al. discloses methods to measure positive ion mass and trace elements in ICP-MS procedures.

Although Houk discloses the analysis of isotopes, Houk does not disclose a kit with isotopes for the analysis of tagged biologically active materials. Houk does not disclose any tagging.. As discussed above, the claims are not obvious with regard to Cais and Foster because neither Cais nor Foster provide kits with isotopes. In addition, Houk does not teach kits useful for tagging with isotopes. Accordingly, the cited references do not provide all the elements of the amended claims. Applicants request that the rejection be withdrawn.

#### ***V. Crooke:***

The Examiner rejected to claims 22 and 26-27 on the basis of obviousness with regard to Cais in view of Foster et al. and Crooke. The Examiner states that Crooke discloses the use of a “plurality” of tagged transition elements and biologically active materials.

The method of Crooke teaches ionization of the entire tagged biomolecule and not just the tag element itself, as in the present application. Applicant’s claimed invention is clearly distinguished from the method of Crooke because only the tag element is measured in the present method (not the tagged biomolecule). As discussed above, the claims are not obvious

with regard to Cais and Foster because neither Cais nor Foster provide kits with isotopes. Crooke does not teach kits with isotopes. Accordingly, the cited references do not provide all the elements of the amended claims. Applicants request that the rejection be withdrawn.

***VI. Mire-Sluis et al.***

The Examiner rejected to claim 28 on the basis of obviousness with regard to Cais in view of Foster and Mire-Sluis. Mire-Sluis disclose assays for cytokines. As discussed above, the claims are not obvious with regard to Cais and Foster because neither Cais nor Foster provide kits with isotopes. Mire-Sluis does not teach kits with isotopes. Accordingly, the cited references do not provide all the elements of the amended claims.

**CONCLUSION**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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